

Hierarchical ER-leap 6th attempt

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Abstract

Abstract text begins here...

1 HiERLeap

1.1 Equivalent Markov Process

From the ER-leap paper, the giant matrix $(\hat{W})^L$ (where \hat{W} appears in the Master Equation) is:

$$\begin{aligned} \left[\prod_{k=L-1 \searrow 0} \hat{W} \right]_{I_L, I_0} &= \sum_{\{I_k | k=1 \dots L-1\}} \left[\prod_{k=L-1 \searrow 0} \hat{W}_{I_{k+1}, I_k} \right] \\ &= \sum_{\{I_k | k=1 \dots L-1\}} \sum_{\{r_k\}} \prod_{k=L-1 \searrow 0} \left[\rho_{r_k} \hat{S}_{I_{k+1}, I_k}^{(r_k)} F_{I_k}^{(r_k)} \right] \end{aligned}$$

where ρ are reaction rates, F are combinatorial factors, and S represents the sparsity structure of state transitions under reactions. Likewise,

$$\begin{aligned} \left[\prod_{k=L-1 \searrow 0} \hat{W} \exp(-\tau_k D) \right]_{I_L, I_0} &= \sum_{\{I_k | k=1 \dots L-1\}} \left[\prod_{k=L-1 \searrow 0} \hat{W}_{I_{k+1}, I_k} \exp(-\tau_k D_{I_k}) \right] \\ &= \sum_{\{I_k | k=1 \dots L-1\}} \sum_{\{r_k\}} \prod_{k=L-1 \searrow 0} \left[\hat{W}_{I_{k+1}, I_k} \exp(-\tau_k D_{I_k}) \right] \end{aligned}$$

$$\begin{aligned}
 &= \sum_{\{I_k | k=1 \dots L-1\}} \sum_{\{r_k\}} \prod_{k=L-1 \searrow 0} \left[\rho_{r_k} \hat{S}_{I_{k+1} J_k}^{(r_k)} F_{I_k}^{(r_k)} \exp(-\tau_k D_{I_k}) \right] \\
 &= \sum_{\{r_k\}} \left(\sum_{\{I_k | k=1 \dots L-1\}} \hat{S}_{I_{k+1} J_k}^{(r_k)} \right) \prod_{k=L-1 \searrow 0} \left[\rho_{r_k} F_{I_k}^{(r_k)} \exp(-\tau_k D_{I_k}) \right]
 \end{aligned}$$

The factor

$$\sum_{\{I_k | k=1 \dots L-1\}} \hat{S}_{I_{k+1} J_k}^{(r_k)}$$

together with the constraint $\sum_I \hat{S}_{I,J}^{(r)} = 1$ means that I_k may be replaced by a unique function value $I_k(\mathbf{R}, I_0)$:

$$\left[\prod_{k=L-1 \searrow 0} \hat{W} \exp(-\tau_k D) \right]_{I_L, J_0} = \sum_{\{r_k\}} \prod_{k=L-1 \searrow 0} \rho_{r_k} F_{I_k(\mathbf{R}, I_0)}^{(r_k)} \exp(-\tau_k D_{I_k(\mathbf{R}, I_0)}) \quad (1)$$

1.2 Hierarchical notation

Hierarchical versions of the reaction, r :

$$r \rightarrow R = (r_1, r_2)$$

This notation is easily extended to any number of levels, eg. $r \rightarrow R = (r_1, \dots, r_\omega)$. But for simplicity we will work with two levels.

$$D_{I_k(\mathbf{R}, I_0)} = \sum_{r_1 \in \{r_1\}} D_{I_k(\mathbf{R}, I_0^{r_1})}^{r_1}$$

1.3 Averaging over reaction orderings

We develop the method for averaging any function f of reaction choice vector \mathbf{r} over reaction order orderings or permutations, σ .

1.3.1 Nonhierarchical:

$$\sum_{\{r_k | k=1 \dots L-1\}} f(\mathbf{r}) = \sum_{\{s | s_r \in \mathbb{N}, \sum_r s_r = L\}} \sum_{\{\sigma | \sigma \text{ permutes unequal } r' s | s\}} f(\mathbf{r}) = \sum_{\{s | L\}} \sum_{\{\sigma | s\}} f(\mathbf{r})$$

$$\sum_{\{\sigma \mid \sigma \text{ permutes unequal } r' \text{ s } \mid s\}} 1 = \# \text{ perms compatible with } s = \begin{pmatrix} L \\ s_1 \dots s_z \end{pmatrix}$$

$$\sum_{\{r_k \mid k=1 \dots L-1\}} f(\mathbf{r}) = \sum_{\{s \mid L\}} \begin{pmatrix} L \\ s_1 \dots s_z \end{pmatrix} \langle f(\mathbf{r}) \rangle_{\{\sigma \mid s\}}$$

Decompose f into permutation-invariant and permutation-variant factors:

$$f(\mathbf{r}(s, \sigma)) = f_1(s) f_2(\mathbf{r}(s, \sigma))$$

Then

$$\sum_{\{r_k \mid k=1 \dots L-1\}} f(\mathbf{r}) = \sum_{\{s \mid L\}} \begin{pmatrix} L \\ s_1 \dots s_z \end{pmatrix} f_1(s) \langle f_2(\mathbf{r}(s, \sigma)) \rangle_{\{\sigma \mid s\}} \quad (2)$$

Example

In the ER-leap paper, this method was used in calculating $\sum_{\{r_k \mid k=1 \dots L-1\}} e(\mathbf{r})$:

$$\begin{aligned} \sum_{\{r_k \mid k=1 \dots L-1\}} e_1(\sigma(\mathbf{r})) e_2(\sigma(\mathbf{r})) &= \sum_{\{s \mid s_r \in \mathbb{N}, \sum_r s_r = L\}} \tilde{e}_1(s(\mathbf{r})) \sum_{\{\sigma \mid \sigma \text{ permutes unequal } r' \text{ s } \mid s\}} e_2(\sigma(\mathbf{r})) \\ &= \sum_{\{s \mid s_r \in \mathbb{N}, \sum_r s_r = L\}} \tilde{e}_1(s(\mathbf{r})) \left(\sum_{\{\sigma \mid \sigma \text{ permutes unequal } r' \text{ s } \mid s\}} e_2(\sigma(\mathbf{r})) \right) \\ &= \sum_{\{s \mid s_r \in \mathbb{N}, \sum_r s_r = L\}} \tilde{e}_1(s(\mathbf{r})) \begin{pmatrix} L \\ s_1 \dots s_R \end{pmatrix} \langle e_2(\sigma(\mathbf{r})) \rangle_{\{\sigma \text{ permutes unequal } r' \text{ s } \mid s\}} \end{aligned}$$

where

$$\begin{aligned} e_1(\mathbf{r}) &\equiv \left[\prod_{k=L-1 \searrow 0} p_{r_k \mid I_0, L-1} \right] (\tilde{D}_{I_0, L-1})^l \exp \left(- \left(\sum_k \tau_k \right) D_{I_0, L-1} \right) \\ e_2(\mathbf{r}) &\equiv \prod_{k=L-1 \searrow 0} \left(\left(\frac{F_{I_k, J_0}^{(r_k)}}{\tilde{F}_{I_0, L-1}^{(r_k)}} \right) \exp \left(-\tau_k (D_{I_k, J_0, J_k}(\mathbf{r}, J_0) - D_{I_0, L-1}) \right) \right). \end{aligned}$$

1.4 Hierarchical Independent Groups Sampling:

We now want to derive an efficient algorithm to sample L reaction events and τ from independent groups of reactions in parallel. If we can achieve this, we may be able to concoct an independent model which is an approximate, upper bound of our desired model. We can then use rejection sampling and samples generated from this approximating distribution to sample from our desired distribution.

1.4.1 Algebraic Manipulation

XXX Define $\mathbf{R}(u, \sigma)$, $u(R)$, $L(u)$, etc.

We start with

$$\left[\prod_{k=L-1 \searrow 0} \hat{W} \exp(-\tau_k D) \right]_{I_L J_0} = \sum_{\{r_k\}} \prod_{k=L-1 \searrow 0} \rho_{r_k} F_{I_k(RJ_0)}^{(r_k)} \exp(-\tau_k D_{I_k(RJ_0)}) .$$

First, we can restrict each group to use an independent subset of species $I_k^{r_1}$. This is possible because reaction independence implies the propensities in group r_1 are unchanged regardless of activity in all other groups. This implies that input species to any reaction in r_1 are not changed by any reaction outside of r_1 . Therefore, we can treat $I_k^{r_1}$ as independent. In the following it is implied that each reaction is indexed by group $r_k = (r_1 r_2)$.

$$= \sum_{\{r_k\}} \prod_{k=L-1 \searrow 0} \frac{\rho_{r_k} F_{I_k^{r_1}(RJ_0^{r_1})}^{(r_k)}}{D_{I_k^{r_1}(RJ_0^{r_1})}^{r_1}} \frac{D_{I_k^{r_1}(RJ_0^{r_1})}^{r_1}}{\tilde{D}^{r_1}(\mathbf{n}_0, L)} \tilde{D}^{(r_1)}(\mathbf{n}_0, L) \exp(-\tau_k (D_{I_k(RJ_0)} - D(\mathbf{n}_0, L))) \exp(-\tau_k D(\mathbf{n}_0, L))$$

For notational brevity, we will now write I_k instead of $I_k^{r_1}$, although it is implied that subsets of I_k are independent for each r_1 . We also denote the ordered reactions in group r_1 as $\{r_j \mid r_j \in r_1 \wedge (r_j \text{ ordered wrt } r_k)\}$. This allows us to write the previous equation as

$$= \sum_{\{r_k\}} \exp\left(-\left(\sum_k \tau_k\right) D(\mathbf{n}_0, L)\right) \left[\prod_{k=L-1 \searrow 0} \exp(-\tau_k (D_{I_k(RJ_0)} - D(\mathbf{n}_0, L))) \right] \\ \prod_{r_1} \prod_{\{r_j \mid (r_j \in r_1) \wedge (r_j \text{ ordered wrt } r_k)\}} \frac{\rho_{r_j} F_{I_j(RJ_0^{r_1})}^{(r_j)}}{D_{I_j(RJ_0)}^{r_1}} \frac{D_{I_j(RJ_0)}^{r_1}}{\tilde{D}^{r_1}(\mathbf{n}_0, L)} \tilde{D}^{r_1}(\mathbf{n}_0, L) .$$

Using the averaging permutation trick from ER-leap and discussed in Section 1.3.1, we permute over all ordered reactions between groups without double counting. Each r_1 will have u_i reaction events. The set $\{r_j \mid r_j \in r_1^* \wedge \sum_j r_j^{r_1} = u_*\}$ is all possible reaction event orderings for groups r_1^* such that exactly u_* events occur. The permutation σ is a permutation of all $\{\{r_j \mid \dots\}\}$ s.t. inter-group ordering is preserved. We let

$$\begin{aligned}
 e_1\left(\sum_k \tau_k\right) &= \exp\left(-\left(\sum_k \tau_k\right) \underline{D}(\mathbf{n}_0, L)\right) \\
 e_2(\{r_j \mid r_1\}) &= \prod_{j=u_i-1 \searrow 0} \frac{\rho_{r_j} F_{I_j(\mathbf{R}J_0)}^{(r_j)}}{D_{I_j(\mathbf{R}J_0)}^{r_1}} \\
 e_3(u, \tau, \{\mathbf{R}^{r_1}\}, \sigma) &= \prod_{k=L-1 \searrow 0} \exp(-\tau_k (D_{I_k(\mathbf{R}J_0)} - \underline{D}(\mathbf{n}_0, L))) \frac{D_{I_k(\mathbf{R}J_0)}^{r_1}}{\tilde{D}^{(r_1)}(\mathbf{n}_0, L)}
 \end{aligned}$$

and get

$$\begin{aligned}
 &\left[\prod_{k=L-1 \searrow 0} \hat{W} \exp(-\tau_k D) \right]_{I_L J_0} = \sum_{\{\mathbf{u} \mid \sum u_i = L\}} \binom{L}{u_1 \dots u_z} \\
 &\left\langle \sum_{\left\{r_j \mid r_j \in r_1^* \wedge \sum_j r_j^{r_1^*} = u_*\right\}} e_1\left(\sum_k \tau_k\right) \times e_3(u, \tau, \{\mathbf{R}^{r_1}\}, \sigma) \times \prod_{r_1} e_2(\{r_j \mid r_1\}) \left(\tilde{D}^{(r_1)}(\mathbf{n}_0, L)\right)^{u_{r_1}} \right\rangle_{\{\sigma \mid \mathbf{u}\}}
 \end{aligned}$$

Separating out components independent of σ and possibly $\{r_j\}$

$$\begin{aligned}
 &= \sum_{\{\mathbf{u} \mid \sum u_i = L\}} \binom{L}{u_1 \dots u_z} \left[\prod_{r_1} \left(\tilde{D}^{(r_1)}(\mathbf{n}_0, L)\right)^{u_{r_1}} \right] e_1\left(\sum_k \tau_k\right) \\
 &\sum_{\left\{r_j \mid r_j \in r_1^* \wedge \sum_j r_j^{r_1^*} = u_*\right\}} \left(\prod_{r_1} e_2(\{r_j \mid r_1\}) \right) \langle e_3(u, \tau, \{\mathbf{R}^{r_1}\}, \sigma) \rangle_{\{\sigma \mid \mathbf{u}\}}
 \end{aligned}$$

Expanding out the r_1^* notation.

$$\begin{aligned}
 &= \sum_{\{\mathbf{u} \mid \sum u_i = L\}} \binom{L}{u_1 \dots u_z} \left[\prod_{r_1} \left(\tilde{D}^{(r_1)}(\mathbf{n}_0, L)\right)^{u_{r_1}} \right] e_1\left(\sum_k \tau_k\right) \sum_{\left\{r_j \mid r_j \in r_1^1 \wedge \sum_j r_j^{r_1^1} = u_1\right\}} \left(\sum_{\left\{r_w \mid r_w \in r_1^2 \wedge \sum_w r_w^{r_1^2} = u_2\right\}} \left(\dots \right. \right. \\
 &\left. \left. \sum_{\left\{r_v \mid r_v \in r_1^3 \wedge \sum_v r_v^{r_1^3} = u_z\right\}} \left(\prod_{r_1} e_2(\{r_j \mid r_1\}) \right) \langle e_3(u, \tau, \{\mathbf{R}^{r_1}\}, \sigma) \rangle_{\{\sigma \mid \mathbf{u}\}} \right) \right) \right) \right)
 \end{aligned}$$

And rearranging terms,

$$\begin{aligned}
 &= \sum_{\{u \mid \sum u_i = L\}} \binom{L}{u_1 \dots u_z} \left[\prod_{r_1} \left(\tilde{D}^{(r_1)}(\mathbf{n}_0, L) \right)^{u_{r_1}} \right] e_1 \left(\sum_k \tau_k \right) \sum_{\{r_j \mid r_j \in r_1^1 \wedge \sum_j r_j^1 = u_1\}} \left(e_2(\{r_j \mid r_1^1\}) \right. \\
 &\quad \left. \sum_{\{r_w \mid r_w \in r_1^2 \wedge \sum_w r_w^2 = u_2\}} e_2(\{r_w \mid r_1^2\}) \left(\dots \sum_{\{r_v \mid r_v \in r_1^i \wedge \sum_v r_v^i = u_i\}} e_2(\{r_v \mid r_1^i\}) \langle e_3(u, \tau, \{\mathbf{R}^n\}, \sigma) \rangle_{\{\sigma \mid u\}} \dots \right) \right)
 \end{aligned}$$

1.4.2 Sampling the Distribution

We first observe that sampling from

$$\sum_{\{r_j \mid r_j \in r_1^1 \wedge \sum_j r_j^1 = u_1\}} e_2(\{r_j \mid r_1^1\}) = \sum_{\{r_j \mid r_j \in r_1^1 \wedge \sum_j r_j^1 = u_1\}} \prod_{j=u_1-1 \searrow 0} \frac{\rho_{r_j} F_{I_j}^{(r_j)}(\mathbf{R}, I_0)}{D_{I_j}^{r_1}(\mathbf{R}, I_0)}$$

is the same as sampling from a Markov chain where

$$P(r_{j+1} \mid I_0, r_j \dots r_0) = P(r_{j+1} \mid I_j) = \frac{\rho_{r_j} F_{I_j}^{(r_{j+1})}(\mathbf{R}, I_0)}{D_{I_j}^{r_1}(\mathbf{R}, I_0)}. \quad (3)$$

This can be sampled by drawing u_1 reactions from r_1^1 by repeatedly drawing reactions with probability equal to (Equation 3) for each reaction channel and then updating state I_j . This is exactly the SSA without the time component. Therefore it may be feasible to speed up this sampling by adapting, for example, ER-leap.

Second, we note that as in ER-leap

$$f(\mathbf{u}) = \binom{L}{u_1 \dots u_z} \left[\prod_{r_1} \left(\frac{\tilde{D}^{(r_1)}(\mathbf{n}_0, L)}{\tilde{D}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \right]$$

is the probability distribution for a multinomial and may be sampled as thus.

Thirdly, we consider

$$e_1 \left(\sum_k \tau_k \right) = \exp \left(- \left(\sum_k \tau_k \right) \mathcal{D}(\mathbf{n}_0, L) \right)$$

which may be decomposed, as in ER-leap, into and Erlang and Uniform Simplex distributions

$$= \text{Erlang}\left(\sum_k \tau_k; L, \mathcal{Q}(\mathbf{n}_0, L)\right) \times \text{UniformSimplex}\left(\tau; L, \sum_k \tau_k\right).$$

Finally, we consider

$$\begin{aligned} \langle e_3(u, \tau, \{\mathbf{R}^{r_1}\}, \sigma) \rangle_{\{\sigma \mid u\}} &= \left\langle \prod_{k=L-1 \searrow 0} \exp(-\tau_k (D_{I_k(\mathbf{R}, I_0)} - \mathcal{Q}(\mathbf{n}_0, L))) \frac{D_{I_k(\mathbf{R}, I_0^{r_1})}^{r_1}}{\tilde{D}^{(r_1)}(\mathbf{n}_0, L)} \right\rangle_{\{\sigma \mid u\}} \\ &= \langle \text{Accept}(\{r_k\}, \sigma, \tau, L) \rangle_{\{\sigma \mid u\}} \end{aligned}$$

which can be interpreted as the probability of acceptance for use in rejection sampling.

We can now sample $\sum_k \tau_k$, σ and $\{r_k\}$, accepting with probability $\text{Accept}(\dots)$. Finally, it should also be possible to get a lower bound on $\text{Accept}(\dots)$, enabling us to have an early acceptance step and thus increase efficiency. This lower bound will be derived in another section (XXX derive lower bound).

1.5 Application

We want to apply Equation XXX to Equation 1. First, just apply Equation XXX to Equation 1 :

$$\left[\prod_{k=L-1 \searrow 0} \hat{W} \right]_{I_L, I_0} = \sum_{\{u_i \mid \sum u_i = L\}} \binom{L}{u_1 \dots u_z} \sum_{\{v_j \mid \sum_j v_{r_1 j} = u_i\}} \prod_{r_1} \binom{u_{r_1}}{v_{r_1 1} \dots v_{r_1 w(r_1)}} \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma \mid \sigma \text{ permutes } u, v\}} \quad (4)$$

where

$$E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \equiv \prod_{k=L-1 \searrow 0} \rho_{(R_{\sigma(k)})} F_{I_k(\mathbf{R}, I_0)}^{(R_{\sigma(k)})} \exp(-\tau_k D_{I_k(\mathbf{R}, I_0)}).$$

To go further we will need bounds on the integer molecule numbers in $I_k(\mathbf{R}, I_0)$, i.e. bounds on $\mathbf{n}(\mathbf{R}, \mathbf{n}_0, k)$. These will be developed in Section 1.6, after which we will return to decomposing Equation 4 in Section 1.7.

1.6 Bounds on n

1.6.1 ER-Leap:

$$n_a(\mathbf{r}, \mathbf{n}_0, k) \leq \tilde{n}_a(\mathbf{s}, I_0) \equiv n_a(0) + (L-1) \max_r \{\Delta m'_a\}$$

$$n_a(\mathbf{r}, \mathbf{n}_0, k) \geq \underline{n}_a(\mathbf{s}, I_0) \equiv n_a(0) + (L-1) \min_r \{\Delta m'_a\}$$

whence

$$\begin{aligned}
 F^{(r)}(n_a(\mathbf{r}, I_0, k)) &= F_{I_k(\mathbf{r}, I_0)}^{(r)} \leq F_{I_k(\mathbf{r}, I_0)}^{(r)} \equiv F^{(r)}(\tilde{n}_a(\mathbf{s}, I_0)) = F_{[n_a + (L-1) \min_r \{\Delta m'_a\} \parallel 1 \leq a \leq A]}^{(r)} \\
 F^{(r)}(n_a(\mathbf{r}, I_0, k)) &= F_{I_k(\mathbf{r}, I_0)}^{(r)} \geq \tilde{F}_{I_k(\mathbf{r}, I_0)}^{(r)} \equiv F^{(r)}(\underline{n}_a(\mathbf{s}, I_0)) = F_{[n_a + (L-1) \max_r \{\Delta m'_a\} \parallel 1 \leq a \leq A]}^{(r)}
 \end{aligned} \tag{5}$$

and likewise for $D_{I_k(\mathbf{r}, I_0)L} \equiv \sum_r \rho_r F_{I_k(\mathbf{r}, I_0)L}^{(r)}$:

$$\begin{aligned}
 D_{I_k(\mathbf{r}, I_0)} &\leq \underline{D}_{I_k(\mathbf{r}, I_0)} \equiv D(\tilde{n}_a(\mathbf{s}, I_0)) = D_{[n_a + (L-1) \min_r \{\Delta m'_a\} \parallel 1 \leq a \leq A]} \\
 D_{I_k(\mathbf{r}, I_0)} &\geq \tilde{D}_{I_k(\mathbf{r}, I_0)} \equiv D(\underline{n}_a(\mathbf{s}, I_0)) = D_{[n_a + (L-1) \max_r \{\Delta m'_a\} \parallel 1 \leq a \leq A]} .
 \end{aligned}$$

The relevant factorization is

$$F^{(r)}(n_a(\mathbf{r}, I_0, k)) = F^{(r)}(\tilde{n}_a(\mathbf{s}, I_0)) \left(\frac{F^{(r)}(n_a(\mathbf{r}, I_0, k))}{F^{(r)}(\tilde{n}_a(\mathbf{s}, I_0))} \right)$$

and

$$\exp[-\tau_k D(n_a(\mathbf{r}, \mathbf{n}_0, k))] = \exp[-\tau_k D(\underline{n}_a(\mathbf{s}, \mathbf{n}_0))] \exp[-\tau_k (D(n_a(\mathbf{r}, \mathbf{n}_0, k)) - D(\underline{n}_a(\mathbf{s}, \mathbf{n}_0)))] .$$

1.6.2 HiER-Leap fine-scale bounds

Recall $a \rightarrow A = (a_1, a_2)$ and $r \rightarrow R = (r_1, r_2)$. We need some near-factorization of Δm_a^r , to separate the spatial scales. We try:

$$\Delta m_A^R = \sum_{\text{"slots"}_\alpha} (C_{a_1 \alpha}^{r_1}) (\Delta m_{a_2 \alpha}^{r_2})$$

Then as in ER-leap,

$$n_A(\mathbf{r}, \mathbf{n}_0, k) \leq \tilde{n}_A(\mathbf{r}, \mathbf{n}_0, L) \equiv n_A(0) + (L-1) \max_R \{\Delta m_A^R\}$$

where

$$\tilde{n}_A(\mathbf{r}, \mathbf{n}_0, L) \equiv n_A(0) + (L-1) \max_{r_1, r_2} \left\{ \sum_\alpha C_{a_1 \alpha}^{r_1} \Delta m_{a_2 \alpha}^{r_2} \right\} . \tag{6}$$

Likewise

$$n_a(\mathbf{r}, \mathbf{n}_0, k) \geq \underline{n}_a(\mathbf{r}, \mathbf{n}_0, L)$$

where

$$\underline{n}_A(\mathbf{r}, \mathbf{n}_0, L) \equiv n_A(0) + (L-1) \min_{r_1, r_2} \left\{ \sum_\alpha C_{a_1 \alpha}^{r_1} \Delta m_{a_2 \alpha}^{r_2} \right\} \tag{7}$$

Unfortunately, these bounds are very coarse: they don't depend on \mathbf{u} or \mathbf{v} .

1.6.3 HiER-Leap block-scale bounds

We seek

$$n_A(\mathbf{r}, \mathbf{n}_0, k) \leq \bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L)$$

Idea: The increase in propensity of a reaction in block r_1 depends on the maximal number of reactions $u_{r_1'}$ that can happen in neighboring reaction blocks r_1' , possibly including r_1 . Thus

$$\begin{aligned} \bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) &\equiv n_A(0) + \sum_{r_1'} \min(u_{r_1'} - \delta_{r_1 r_1'}, L - 1) \max_{r_2'} \{ \Delta m_{(a_1 a_2)}^{(r_1' r_2')} \} \\ &= n_A(0) + \sum_{r_1'} \min(u_{r_1'} - \delta_{r_1 r_1'}, L - 1) \max_{r_2'} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \\ &= n_A(0) + \sum_{r_1'} \min(u_{r_1'} - \delta_{r_1 r_1'}, L - 1) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \end{aligned}$$

Lemma 1: If $u_{r_1} \geq 1$, then we can drop the $\min(\dots, L - 1)$ and obtain in this case :

$$\bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) = n_A(0) + \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\}. \quad (8)$$

In other words, to bound the propensities of any reaction that might actually happen, we can use Equation 8. The only place we can't use this simplification is when calculating the propensity of a reaction that will not happen in the next L reaction events, because some other single reaction block r_1' will capture all L events. So we can take Equation 8 to bound the propensity of any reaction that may occur in reaction block r_1 .

Proof: If $r_1 = r_1'$, then $\delta_{r_1 r_1'} = 1$ so $u_{r_1'} \leq L \Rightarrow u_{r_1'} - \delta_{r_1 r_1'} \leq L - 1$. On the other hand if $r_1 \neq r_1'$, then $\delta_{r_1 r_1'} = 0$ and also $u_{r_1'} + u_{r_1} \leq \sum_{r_1} u_{r_1} = L \Rightarrow u_{r_1'} \leq L - u_{r_1} \leq L - 1 \Rightarrow u_{r_1'} - \delta_{r_1 r_1'} = u_{r_1'} \leq L - 1$. Either way, $u_{r_1'} - \delta_{r_1 r_1'} \leq L - 1$ so $\min(u_{r_1'} - \delta_{r_1 r_1'}, L - 1) = (u_{r_1'} - \delta_{r_1 r_1'})$.

Likewise

$$n_A(\mathbf{r}, \mathbf{n}_0, k) \geq \underline{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) \equiv n_A(0) + \sum_{r_1'} \min(u_{r_1'} - \delta_{r_1 r_1'}, L - 1) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \min_{r_2} \Delta m_{a_2 \alpha}^{r_2'} \right\}$$

but if $u_{r_1} \geq 1$, we have

$$n_A(\mathbf{r}, \mathbf{n}_0, k) \geq \underline{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) = n_A(0) + \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \min_{r_2} \Delta m_{a_2 \alpha}^{r_2'} \right\}. \quad (9)$$

Next we calculate the bounds

$$\begin{aligned}
 \bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) &\leq \max_{\{u | \sum u = L \wedge u_{r_1} \geq 1\}} \bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) \\
 &= n_A(0) + \max_{\{u | \sum u = L \wedge u_{r_1} \geq 1\}} \sum_{r_1'} \min(u_{r_1'} - \delta_{r_1 r_1'}, L - 1) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \\
 &= n_A(0) + \max_{\{u | \sum u = L \wedge u_{r_1} \geq 1\}} \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\}
 \end{aligned}$$

by Lemma 1. But

$$\begin{aligned}
 \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} &\leq \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \max_{r_1''} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1''} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \\
 &\leq \left(\max_{r_1''} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1''} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \right) \left(\sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \right) \\
 &\leq \left(\max_{r_1'} \max_{r_2'} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \right) (L - 1)
 \end{aligned}$$

which is independent of \mathbf{u} . Thus

$$\bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) \leq n_A(0) + (L - 1) \left(\max_{r_1'} \max_{r_2'} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \right) = \tilde{n}_A(\mathbf{n}_0, L)$$

with the last equality following from Equation 6. A similar calculation applies to \underline{n} . Thus,

Theorem 1. For $0 \leq k \leq L - 1$,

$$\underline{n}_{A r_1}(\mathbf{n}_0, L) \leq \underline{n}_{A r_1}(\mathbf{u}(\mathbf{R}), \mathbf{n}_0, L) \leq n_A(\mathbf{R}, \mathbf{n}_0, k) \leq \bar{n}_{A r_1}(\mathbf{u}(\mathbf{R}), \mathbf{n}_0, L) \leq \tilde{n}_A(\mathbf{n}_0, L). \quad (10)$$

1.6.4 Bounds on F and D

Since F is monotonic, if $[\mathbf{R}]_k = R = (r_1 r_2)$,

$$\begin{aligned}
 F_{I_k(\mathbf{R}, I_0)}^{(R)} &= F^{(R)}(\mathbf{n}(\mathbf{R}, \mathbf{n}_0, k)) \\
 &\leq F^{(r_1 r_2)}(\bar{n}_{* r_1}(\mathbf{u}(\mathbf{R}), \mathbf{n}_0, L)) \equiv \bar{F}^{(r_1 r_2)}(\mathbf{u}(\mathbf{R}), \mathbf{n}_0, L) \\
 &\leq F^{(r_1 r_2)}(\tilde{\mathbf{n}}(\mathbf{n}_0, L)) \equiv \tilde{F}^{(r_1 r_2)}(\mathbf{n}_0, L)
 \end{aligned}$$

Thus if $[\mathbf{R}]_k = R = (r_1 r_2)$,

$$F^{(R)}(\mathbf{n}(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) \leq \bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) \leq \tilde{F}^{(r_1 r_2)}(\mathbf{n}_0, L(u))$$

where

$$\begin{aligned}\bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) &\equiv F^{(r_1 r_2)}(\bar{\mathbf{n}}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) \\ \tilde{F}^{(r_1 r_2)}(\mathbf{n}_0, L) &\equiv F^{(r_1 r_2)}(\tilde{\mathbf{n}}(\mathbf{n}_0, L)).\end{aligned}$$

Likewise if $[\mathbf{R}]_k = R = (r_1 r_2)$,

$$F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) \geq \underline{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) \geq \underline{F}^{(r_1 r_2)}(\mathbf{n}_0, L(u))$$

where

$$\begin{aligned}\underline{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) &\equiv F^{(r_1 r_2)}(\underline{\mathbf{n}}_{Ar_1}(\mathbf{u}, \mathbf{n}_0, L)) \\ \underline{F}^{(r_1 r_2)}(\mathbf{n}_0, L) &\equiv F^{(r_1 r_2)}(\underline{\mathbf{n}}_A(\mathbf{n}_0, L)).\end{aligned}$$

Summing over a block of reactions,

$$\begin{aligned}D^{(r_1)}(\mathbf{n}) &\equiv \sum_{r_2} \rho_{r_1 r_2} F^{(r_1 r_2)}(\mathbf{n}) \\ D(\mathbf{n}) &\equiv \sum_{r_1 r_2} \rho_{r_1 r_2} F^{(r_1 r_2)}(\mathbf{n}) = \sum_{r_1} D^{(r_1)}(\mathbf{n})\end{aligned}\tag{11}$$

Note also

$$\begin{aligned}\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) &= D^{(r_1)}(\bar{\mathbf{n}}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) \\ \tilde{D}^{(r_1)}(\mathbf{n}_0, L) &= D^{(r_1)}(\tilde{\mathbf{n}}(\mathbf{n}_0, L)).\end{aligned}$$

Using monotonicity of $F^{(r_1 r_2)}(\mathbf{n}_{Ar_1})$, $D^{(r_1)}(\mathbf{n})$ and $D(\mathbf{n})$ as a function of \mathbf{n}_A , we deduce:

Theorem 2. If $[\mathbf{R}]_k = R = (r_1 r_2)$, we have the following bounds:

$$\bar{D}^{(r_1)}(\mathbf{n}_0, L(u)) \leq \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \leq D^{(r_1)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) \leq \bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \leq \tilde{D}^{(r_1)}(\mathbf{n}_0, L)$$

where

$$\begin{aligned}\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \sum_{r_2} \rho_{r_1 r_2} \bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L), \quad \tilde{D}^{(r_1)}(\mathbf{n}_0, L(u)) \equiv \sum_{r_2} \rho_{r_1 r_2} \tilde{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L), \\ \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \sum_{r_2} \rho_{r_1 r_2} \underline{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L), \quad \underline{D}^{(r_1)}(\mathbf{n}_0, L(u)) \equiv \sum_{r_2} \rho_{r_1 r_2} \underline{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L);\end{aligned}$$

Likewise

$$\bar{D}(\mathbf{n}_0, L(u)) \leq \underline{D}(\mathbf{u}, \mathbf{n}_0, L) \leq D(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) \leq \bar{D}(\mathbf{u}, \mathbf{n}_0, L) \leq \tilde{D}(\mathbf{n}_0, L(u))$$

where

$$\begin{aligned}
 \bar{D}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \sum_{r_1 r_2} \rho_{r_1 r_2} \bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) = \sum_{r_1} \bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L), \\
 \check{D}(\mathbf{n}_0, L(u)) &\equiv \sum_{r_1 r_2} \rho_{r_1 r_2} \check{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) = \sum_{r_1} \check{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L), \\
 \underline{D}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \sum_{r_1 r_2} \rho_{r_1 r_2} \underline{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) = \sum_{r_1} \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L), \\
 \underline{D}(\mathbf{n}_0, L(u)) &\equiv \sum_{r_1 r_2} \rho_{r_1 r_2} \underline{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) = \sum_{r_1} \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L).
 \end{aligned}$$

Proof: Calculations above.

1.6.5 Optimized HiER-Leap block-scale bounds on D

At the block level, better bounds than \underline{D} and \bar{D} are possible because of constraints on the simultaneous minimization or maximization of propensities of many reactions in a block.

Failed attempt. This bound didn't produce strong enough inequalities to make a good algorithm.

$$\begin{aligned}
 \check{D}^{(r_1)}(\mathbf{n}_0, L(u)) &\equiv \max_{\{u, v | \sum u = L \wedge \sum v = u \wedge u_{r_1} \geq 1\}} \max_{\{\sigma | u, v\}} \sum_{r_2} \rho_{r_1 r_2} F^{(r_1 r_2)}(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, L) \\
 &= D^{(r_1)}(\check{\mathbf{n}}_{r_1}(\mathbf{n}_0, L))
 \end{aligned}$$

where

$$\begin{aligned}
 \check{\mathbf{n}}_{r_1}(\mathbf{n}_0, L) &\equiv \mathbf{n}(\mathbf{R}(\mathbf{u}_{r_1}^*, \mathbf{v}_{r_1}^*, \sigma_{r_1}^*), \mathbf{n}_0, k), \text{ where} \\
 (\mathbf{u}_{r_1}^*, \mathbf{v}_{r_1}^*, \sigma_{r_1}^*) &\equiv \operatorname{argmax}_{\{u, v, \sigma | \sum u = L \wedge \sum v = u \wedge u_{r_1} \geq 1 \wedge \sigma \text{ respects } v\}} \sum_{r_2} \rho_{r_1 r_2} F^{(r_1 r_2)}(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, L). \quad (12)
 \end{aligned}$$

XXX express " σ respects v " algebraically XXX

Lemma 2. $\check{\mathbf{n}}_{r_1}(\mathbf{n}_0, L) \leq \max_{\{u | \sum u = L \wedge u_{r_1} \geq 1\}} \bar{\mathbf{n}}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L)$.

XXX Questions: Can we get enough inequalities on D rather than n ?

What if we try instead:

$$\check{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L(u)) \equiv \max_{\{v | \sum v = u\}} \max_{\{\sigma | u, v\}} \sum_{r_2} \rho_{r_1 r_2} F^{(r_1 r_2)}(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, L) ?$$

Can we relax the \equiv equality to an inequality that preserves $\check{\mathbf{n}}_{r_1}(\mathbf{n}_0, L) \leq \bar{\mathbf{n}}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L)$?

XXX

Better attempt.

Consider

$$D^{(r_1)}(\bar{\mathbf{n}}_{* r_1}(\mathbf{u}, \mathbf{n}_0, L)) = \sum_{r_2} \rho_{r_1 r_2} F^{(r_1 r_2)}(\bar{\mathbf{n}}_{* r_1}(\mathbf{u}, \mathbf{n}_0, L)) = \sum_{r_2} \rho_{r_1 r_2} \bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L) = \bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L).$$

Define

$$\begin{aligned}\hat{D}^{(r_1)}(\mathbf{n}_0, L(u)) &\equiv \max_{\{u|\sum u=L \wedge u_{r_1} \geq 1\}} D^{(r_1)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) \\ &= D^{(r_1)}(\hat{n}_{r_1}(\mathbf{n}_0, L))\end{aligned}$$

where we define

$$\begin{aligned}\hat{n}_{r_1}(\mathbf{n}_0, L) &\equiv \bar{n}_{*r_1}(\hat{\mathbf{u}}, \mathbf{n}_0, L), \text{ where} \\ \hat{\mathbf{u}} &\equiv \operatorname{argmax}_{\{u|\sum u=L \wedge u_{r_1} \geq 1\}} D^{(r_1)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)).\end{aligned}\tag{13}$$

Now we get useable inequalities:

Lemma 2. For all r_1, A , and \mathbf{u} such that $u_{r_1} \geq 1$, $\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \leq \hat{D}^{(r_1)}(\mathbf{n}_0, L(u))$.

Proof: $\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \leq \max_{\{u|\sum u=L \wedge u_{r_1} \geq 1\}} D^{(r_1)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) = \hat{D}^{(r_1)}(\mathbf{n}_0, L(u))$.

However, we do *not* know that for all r_1, A , and \mathbf{u} such that $u_{r_1} \geq 1$, $\bar{n}_{Ar_1}(\mathbf{u}, \mathbf{n}_0, L) \leq \hat{n}_{Ar_1}(\mathbf{n}_0, L)$, even though $D(n)$ is monotonic in each component of \mathbf{n} , since \hat{D} allows for tradeoffs between different components of \mathbf{n} .

Lemma 3. For all r_1 and A , $\hat{n}_{Ar_1}(\mathbf{n}_0, L) \leq \tilde{n}_A(\mathbf{n}_0, L)$.

Proof: By Equation 13,

$$\hat{n}_{Ar_1}(\mathbf{n}_0, L) = \bar{n}_{*r_1}(\hat{\mathbf{u}}, \mathbf{n}_0, L)$$

where $\hat{u}_{r_1} \geq 1$. Then as in the proof of Theorem 1 above (qv. for details omitted here),

$$\begin{aligned}\bar{n}_{*r_1}(\hat{\mathbf{u}}, \mathbf{n}_0, L) &\leq \max_{\{u|\sum u=L \wedge u_{r_1} \geq 1\}} \bar{n}_{Ar_1}(\mathbf{u}, \mathbf{n}_0, L) \\ &= n_A(0) + \max_{\{u|\sum u=L \wedge u_{r_1} \geq 1\}} \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{j_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \\ &\leq \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \max_{r_1''} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1''} \max_{j_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \\ &\leq \left(\max_{r_1'} \max_{r_2'} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \right) (L-1)\end{aligned}$$

Thus

$$\hat{n}_{Ar_1}(\mathbf{n}_0, L) \leq n_A(0) + (L-1) \left(\max_{r_1'} \max_{r_2'} \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \right) = \tilde{n}_A(\mathbf{n}_0, L),$$

QED.

XXX Question: Can we relax the \equiv equality to an inequality that preserves $\hat{n}_{Ar_1}(\mathbf{n}_0, L) \leq \tilde{n}_A(\mathbf{n}_0, L)$? Then optimization would not have to be as thorough; any improvement would help. Eg. $\hat{n} = \bar{n}(\hat{\mathbf{u}})$, $\hat{\mathbf{u}} = \hat{\mathbf{u}}(\mathbf{u})$ is an “algorithmic improvement” such that $D^{(r_1)}(n(u)) \leq D^{(r_1)}(\bar{n}(\hat{\mathbf{u}})) \leq D^{(r_1)}(\bar{n}(\hat{\mathbf{u}}^*))$ where $\hat{\mathbf{u}}^* = \operatorname{argmax}_{\hat{\mathbf{u}}} D^{(r_1)}(\bar{n}(\hat{\mathbf{u}}))$.
? XXX

By monotonicity of $D^{(r_1)}(n)$, as in Theorem 2, we deduce:

Theorem 3: If $[\mathbf{R}]_k = R = (r_1 \ r_2)$, we have the following bounds:

$$\begin{aligned} \underline{D}^{(r_1)}(\mathbf{n}_0, L(u)) &\leq \underline{D}^{(r_1)}(\mathbf{n}_0, L(u)) \leq \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \\ &\leq D^{(r_1)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) \\ &\leq \overline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \leq \hat{D}^{(r_1)}(\mathbf{n}_0, L(u)) \leq \check{D}^{(r_1)}(\mathbf{n}_0, L(u)) \end{aligned}$$

Proof: Calculations above.

XXX check this ; elaborate slightly ? XXX

We also define global versions of \hat{D} and \check{D} :

$$\begin{aligned} \hat{D}(\mathbf{n}_0, L) &\equiv \sum_{r_1} \hat{D}^{(r_1)}(\mathbf{n}_0, L) \\ \check{D}(\mathbf{n}_0, L) &\equiv \sum_{r_1} \check{D}^{(r_1)}(\mathbf{n}_0, L) \end{aligned}$$

And of course $D(n) = \sum_{r_1} D^{(r_1)}(n)$, from Equation 13 XXX.

1.7 Using bounds on D and F

In what follows, the easy version of the algorithm takes $\hat{D}^{(r_1)} = \check{D}^{(r_1)}$ and $\underline{D}^{(r_1)} = \overline{D}^{(r_1)}$, so that no optimization or nontrivial bounds are required. Given that algorithm, it would be possible to observe the multinomial in \mathbf{u} and compare it to the actual distribution of \mathbf{u} 's (eg from repeated restarts of SSA) to see if one can learn to predict a better multinomial on \mathbf{u} from the hypothetical one and other easily calculated quantities.

Alternatively and more elaborately, $\hat{D}^{(r_1)}$ in the following may be interpreted as anything bounded to be between the actual $\hat{D}^{(r_1)}$ and $\check{D}^{(r_1)}$, and likewise for $\underline{D}^{(r_1)}$. For example, various relaxed optimizations are possible by dividing reaction blocks into fast/slow, nearby/distant, etc., and using the trivial L bound on \mathbf{u} for the slow or distant blocks which should be in the great majority so that the remaining optimization problem can be solved easily.

XXX Still working here.

In Equation 4,

$$\begin{aligned} \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma | \mathbf{u}, \mathbf{v}\}} &\equiv \left\langle \prod_{k=L-1 \searrow 0} \rho_{(R_{\sigma(k)})} F_{I_k}^{(R_{\sigma(k)})}(\mathbf{R}_{I_0}) \exp(-\tau_k D_{I_k}(\mathbf{R}_{I_0})) \right\rangle_{\{\sigma | \sigma \text{ permutes } \mathbf{u}, \mathbf{v}\}} \\ &= \left\langle \prod_{k=L-1 \searrow 0} \rho_{(R_{\sigma(k)})} F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) \exp(-\tau_k D(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))) \right\rangle_{\{\sigma | \mathbf{u}, \mathbf{v}\}} \\ &= \end{aligned}$$

$$\begin{aligned}
 & \left\langle \prod_{k=L-1 \searrow 0} \left(\frac{F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))}{\bar{F}^{(r_1 \ r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \frac{\rho_{(R_{\sigma(k)})} \bar{F}^{(r_1 \ r_2)}(\mathbf{u}, \mathbf{n}_0, L)}{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)} \frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\hat{D}^{(r_1)}(\mathbf{n}_0, L(u))} \hat{D}^{(r_1)}(\mathbf{n}_0, L(u)) \right) \right. \\
 & \quad \exp \left\{ -\tau_k \sum_{r_1} [D^{(r_1)}(\mathbf{n}(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)] \right\} \\
 & \quad \left. \exp \left\{ -\tau_k \sum_{r_1} \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right\} \right\rangle_{\{\sigma \mid \mathbf{u}, \mathbf{v}\}}
 \end{aligned}$$

XXX Relate to Section 1.4.1 .

Define

$$\begin{aligned}
 \bar{p}(r_2 \mid r_1, \mathbf{u}) &\equiv \frac{\rho_{(R_{\sigma(k)})} \bar{F}^{(r_1 \ r_2)}(\mathbf{u}, \mathbf{n}_0, L)}{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)} \\
 \hat{p}(r_1) &\equiv \frac{\hat{D}^{(r_1)}(\mathbf{n}_0, L)}{\hat{D}(\mathbf{n}_0, L)} \\
 p_{\wedge}(r_1) &\equiv \frac{D_{\wedge}^{(r_1)}(\mathbf{n}_0, L)}{D_{\wedge}(\mathbf{n}_0, L)}
 \end{aligned}$$

Then

$$\begin{aligned}
 \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma \mid \mathbf{u}, \mathbf{v}\}} &= \left\langle \prod_{k=L-1 \searrow 0} \left(\frac{F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))}{\bar{F}^{(r_1 \ r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right) \bar{p}(r_2 \mid r_1)^{v_R} \right. \\
 & \quad \left(\prod_{r_1} \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)} \right)^{u_{r_1}} \right) \left(\prod_{r_1} \left(\frac{\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{D_{\wedge}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \right) \left(\prod_{r_1} p_{\wedge}(r_1)^{u_{r_1}} \right) D_{\wedge}(\mathbf{n}_0, L)^L \\
 & \quad \prod_{k=L-1 \searrow 0} \exp \left\{ -\tau_k \sum_{r_1} [D^{(r_1)}(\mathbf{n}(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)] \right\} \\
 & \quad \left. \exp \left\{ -\tau_k \sum_{r_1} [\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - D_{\wedge}^{(r_1)}(\mathbf{n}_0, L)] \right\} \exp \left\{ -\tau_k D_{\wedge}(\mathbf{n}_0, L) \right\} \right\rangle_{\{\sigma \mid \mathbf{u}, \mathbf{v}\}}
 \end{aligned}$$

$$\tau(r_1, \mathbf{R}) \equiv \sum_{k \mid r_1} \tau_k$$

$$\tau = \sum_{r_1} \tau(r_1, \mathbf{R})$$

One variant is:

$$\begin{aligned}
 \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma|u,v\}} &= \bar{p}(r_2 | r_1)^{\nu_R} \left\langle \left\langle \prod_{k=L-1 \searrow 0} \left(\frac{F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))}{\bar{F}^{(r_1 \ r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right) \right\rangle_{\{\sigma_2 | u, v\}} \right\rangle \\
 &\quad \left(\prod_{r_1} \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)} \right)^{u_{r_1}} \right) \left(\prod_{r_1} \bar{p}(r_1)^{u_{r_1}} \right) \\
 &\quad \left(\prod_{k=L-1 \searrow 0} \exp \left\{ -\tau_k \sum_{r_1} [D^{(r_1)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)] \right\} \right) \\
 &\quad \left(\prod_{r_1} \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\bar{D}^{(r_1)}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \exp \left\{ -\tau(r_1, \mathbf{R}) [\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - \bar{D}^{(r_1)}(\mathbf{n}_0, L)] \right\} \right) \\
 &\quad \bar{D}(\mathbf{n}_0, L)^L \exp \left\{ -\tau \bar{D}(\mathbf{n}_0, L) \right\} \Bigg\rangle_{\{\sigma_1 | u, v\}}
 \end{aligned}$$

A failed variant invoked $\bar{p}(r_1 | u) = \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) / \underline{D}(\mathbf{u}, \mathbf{n}_0, L)$, which depends on u and therefore is not part of a multinomial.

For the first variant,

$$\begin{aligned}
 \text{Accept}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) &\equiv \left\langle \prod_{k=L-1 \searrow 0} \left(\frac{F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))}{\bar{F}^{(r_1 \ r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right) \exp \left\{ -\tau_k \sum_{r_1} [D^{(r_1)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)] \right\} \right\rangle_{\{\sigma_2 | u, v\}} \quad (14)
 \end{aligned}$$

$$\begin{aligned}
 \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \left\langle \text{Accept}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) \right. \\
 &\quad \left. \prod_{r_1} \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\bar{D}^{(r_1)}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \exp \left\{ -\tau(r_1, \mathbf{R}) [\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - \bar{D}^{(r_1)}(\mathbf{n}_0, L)] \right\} \right\rangle_{\{\sigma_1 | u, v\}} \quad (15)
 \end{aligned}$$

$$M_{\text{coarse}}(\mathbf{n}_0, L) \equiv 1$$

$$M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \equiv \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)} \right)^{u_{r_1}}$$

so

$$\begin{aligned} \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma | \mathbf{u}, \mathbf{v}\}} &= \left(\prod_{r_1} M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right) \left(\prod_{r_1} p(r_1)^{u_{r_1}} \right) \left(\prod_{r_1, r_2} \bar{p}(r_2 | r_1)^{v_R} \right) \\ &\langle \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} D_{\wedge}(\mathbf{n}_0, L)^L \exp \{ -\tau D_{\wedge}(\mathbf{n}_0, L) \} \end{aligned}$$

Then Equation 4 becomes

$$\begin{aligned} \left[\prod_{k=L-1 \searrow 0} \hat{W} \right]_{I_L, I_0} &= M_{\text{coarse}}(\mathbf{n}_0, L) \left(\prod_{r_1} M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right) \\ \sum_{\{u_i | \sum u_i = L\}} \prod_{r_1} \left[\binom{L}{u_1 \dots u_z} \left(\prod_{r_1} p(r_1)^{u_{r_1}} \right) \right] &\sum_{\{v_j | \sum_j v_{r_1, j} = u_i\}} \prod_{r_1} \left(\binom{u_{r_1}}{v_{r_1, 1} \dots v_{r_1, w(r_1)}} \right) \left(\prod_{r_2} \bar{p}(r_2 | r_1)^{v_R} \right) \\ &\langle \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} D_{\wedge}(\mathbf{n}_0, L)^L \exp \{ -\tau D_{\wedge}(\mathbf{n}_0, L) \} \end{aligned}$$

So the core algorithm is

$$\begin{aligned} \left[\prod_{k=L-1 \searrow 0} \hat{W} \right]_{I_L, I_0} &= M_{\text{coarse}}(\mathbf{n}_0, L) \left(\prod_{r_1} M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right) \\ &\text{Multinomial}(\mathbf{u} | \mathbf{p}, L) \left(\prod_{r_1} \text{Multinomial}(\mathbf{v} | \bar{\mathbf{p}}, r_1, u_{r_1}) \right) \\ &\langle \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} \text{Erlang}(\tau | L, D_{\wedge}(\mathbf{n}_0, L)) \text{UniformSimplex} \left(\tau; L, \sum_k \tau_k \right) \end{aligned} \tag{16}$$

where we have used

$$\begin{aligned} \text{Erlang}(\tau | L, D_{\wedge}(\mathbf{n}_0, L)) &= D_{\wedge}(\mathbf{n}_0, L)^L \exp \{ -\tau D_{\wedge}(\mathbf{n}_0, L) \} \\ \text{Multinomial}(\mathbf{u} | \mathbf{p}_{\wedge}, L) &= \binom{L}{u_1 \dots u_z} \left(\prod_{r_1} p(r_1)^{u_{r_1}} \right) \\ \text{Multinomial}(\mathbf{v} | \bar{\mathbf{p}}, r_1, u_{r_1}) &= \binom{u_{r_1}}{v_{r_1, 1} \dots v_{r_1, w(r_1)}} \left(\prod_{r_2} \bar{p}(r_2 | r_1)^{v_R} \right) \end{aligned}$$

XXX Problem: restore ER-Leap's

$$\text{UniformSimplex} \left(\tau; L, \sum_{k=0}^{L-1} \tau_k \right) = 1 / \left(\frac{t^{L-1}}{(L-1)!} \right)$$

$$\text{Erlang}(t; l, \lambda) \equiv \lambda^l e^{-\lambda t} t^{l-1} / (l-1)!$$

where $\langle t \rangle_{\text{Erlang}} = l / \lambda$;

in a hierarchical version.

XXX

1.7.1 Alternative

Another (October 2009) possibility is:

$$\begin{aligned} \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma | u, v\}} &= \bar{p}(r_2 | r_1)^{v_R} \left\langle \left\langle \prod_{k=L-1 \searrow 0} \left(\frac{F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))}{\bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right) \right\rangle_{\{\sigma_2 | u, v\}} \left(\prod_{r_1} \hat{p}(r_1)^{u_{r_1}} \right) \right. \\ &\quad \left(\prod_{k=L-1 \searrow 0} \exp \left\{ -\tau_k \sum_{r_1} [D^{(r_1)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)] \right\} \right) \\ &\quad \left(\prod_{r_1} \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\hat{D}^{(r_1)}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \exp \left\{ -\tau(r_1, \mathbf{R}) [\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - \underline{D}^{(r_1)}(\mathbf{n}_0, L)] \right\} \right) \\ &\quad \left(\frac{\hat{D}(\mathbf{n}_0, L)}{\underline{D}(\mathbf{n}_0, L)} \right)^L \underline{D}(\mathbf{n}_0, L)^L \exp \left\{ -\tau \underline{D}(\mathbf{n}_0, L) \right\} \Bigg\rangle_{\{\sigma_1 | u, v\}} \\ \text{Accept}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) &\equiv \left\langle \prod_{k=L-1 \searrow 0} \left(\frac{F^{(R)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k))}{\bar{F}^{(r_1 r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right) \exp \left\{ -\tau_k \sum_{r_1} [D^{(r_1)}(n(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma), \mathbf{n}_0, k)) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)] \right\} \right\rangle_{\{\sigma_2 | u, v\}} \end{aligned} \quad (17)$$

$$\begin{aligned} \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \left\langle \text{Accept}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) \right. \\ &\quad \left. \prod_{r_1} \left(\frac{\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{\hat{D}^{(r_1)}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \exp \left\{ -\tau(r_1, \mathbf{R}) [\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - \underline{D}^{(r_1)}(\mathbf{n}_0, L)] \right\} \right\rangle_{\{\sigma_1 | u, v\}} \end{aligned} \quad (18)$$

$$M_{\text{coarse}}(\mathbf{n}_0, L) \equiv \left(\frac{\hat{D}(\mathbf{n}_0, L)}{\underline{D}(\mathbf{n}_0, L)} \right)^L$$

$$M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \equiv 1$$

so

$$\begin{aligned} \langle E(\mathbf{R}(\mathbf{u}, \mathbf{v}, \sigma)) \rangle_{\{\sigma | \mathbf{u}, \mathbf{v}\}} &= \left(\prod_{r_1} M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right) \left(\prod_{r_1} \underline{p}(r_1)^{u_{r_1}} \right) \left(\prod_{r_1, r_2} \bar{p}(r_2 | r_1)^{v_{r_2}} \right) \\ &\langle \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} D_{\lambda}(\mathbf{n}_0, L)^L \exp\{-\tau D_{\lambda}(\mathbf{n}_0, L)\} \end{aligned}$$

Then Equation 4 becomes

$$\begin{aligned} \left[\prod_{k=L-1 \searrow 0} \hat{W} \right]_{I_L, I_0} &= M_{\text{coarse}}(\mathbf{n}_0, L) \left(\prod_{r_1} M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right) \\ \sum_{\{u_i | \sum u_i = L\}} \prod_{r_1} \left[\binom{L}{u_1 \dots u_z} \left(\prod_{r_1} \hat{p}(r_1)^{u_{r_1}} \right) \right] &\sum_{\{v_j | \sum_j v_{r_1, j} = u_i\}} \prod_{r_1} \left(\binom{u_{r_1}}{v_{r_1, 1} \dots v_{r_1, w(r_1)}} \right) \left(\prod_{r_2} \bar{p}(r_2 | r_1)^{v_{r_2}} \right) \\ &\langle \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} D_{\lambda}(\mathbf{n}_0, L)^L \exp\{-\tau D_{\lambda}(\mathbf{n}_0, L)\} \end{aligned}$$

So the alternative core algorithm is

$$\begin{aligned} \left[\prod_{k=L-1 \searrow 0} \hat{W} \right]_{I_L, I_0} &= M_{\text{coarse}}(\mathbf{n}_0, L) \left(\prod_{r_1} M_{\text{fine}(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right) \\ &\text{Multinomial}(\mathbf{u} | \hat{\mathbf{p}}, L) \left(\prod_{r_1} \text{Multinomial}(\mathbf{v} | \bar{\mathbf{p}}, r_1, u_{r_1}) \right) \end{aligned} \quad (19)$$

$$\langle \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} \text{Erlang}(\tau | L, D_{\lambda}(\mathbf{n}_0, L)) \text{UniformSimplex}\left(\tau; L, \sum_k \tau_k\right)$$

The choice among these two variants may be dominated by the difference in rejection rates at the coarse scale.

1.8 Rejection sampling algorithms

We want to implement

$$\begin{aligned} \text{Accept}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) &\equiv \langle P_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \sigma_2, \mathbf{n}_0, L) \rangle_{\{\sigma_2 | \mathbf{u}, \mathbf{v}\}} \\ \text{Accept}_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) &\equiv \langle \text{Accept}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) P_{\text{coarse}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) \rangle_{\{\sigma_1 | \mathbf{u}, \mathbf{v}\}} \end{aligned}$$

1.8.1 ER-Leap rejection sampling

In ER-Leap we found a function $\underline{A}(x)$ such that

$$0 \leq \underline{A}(x) \leq \text{Accept}(x) \equiv P(x) / (M P'(x)) < 1$$

$\text{Accept}(x) = \underline{A}(x) \cdot 1 + (1 - \underline{A}(x)) \cdot Q(x)$, where

$$Q(x) \equiv \left(\frac{\text{Accept}(x) - \underline{A}(x)}{1 - \underline{A}(x)} \right),$$

where

$$\text{Accept}(s, l, \tau) = \langle P_\sigma \rangle_{\{\sigma|s\}}$$

$P_\sigma = \underline{P} \cdot 1 + (1 - \underline{P}) \cdot Q_\sigma$, where

$$Q_\sigma = \left(\frac{P_\sigma - \underline{P}}{1 - \underline{P}} \right) \leq 1$$

$$\underline{P} \left(s, \sum_k \tau_k, L \right) \equiv \left[\prod_{r=1}^R \left(\frac{\underline{F}_{l_0, L-1}^{(r)}}{\bar{F}_{l_0, L-1}^{(r)}} \right)^{s_r} \right] \exp \left(- \left(\sum_k \tau_k \right) (\tilde{D}_{l_0, L-1} - D_{l_0, L-1}) \right)$$

and thus

$$\langle P_\sigma \rangle_{\{\sigma|s\}} = \underline{P} \cdot 1 + (1 - \underline{P}) \cdot \langle Q_\sigma \rangle_{\{\sigma|s\}}$$

1.8.2 HiER-Leap rejection sampling

Now we want $\underline{A}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L)$ XXX missing time tau from arg list

$$\begin{aligned} \underline{A}_{\text{fine}}(\mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) &= \prod_R \left(\frac{\underline{F}^{(r_1, r_2)}(\mathbf{u}, \mathbf{n}_0, L)}{\bar{F}^{(r_1, r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right)^{v(R)} \exp \left\{ -\tau_k \left[\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right] \right\} \\ &= \prod_{r_1} \underline{A}_{\text{fine}}(r_1, \mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) \end{aligned}$$

$$\underline{A}_{\text{fine}}(r_1, \mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) \equiv \left(\prod_{r_2} \left(\frac{\underline{F}^{(r_1, r_2)}(\mathbf{u}, \mathbf{n}_0, L)}{\bar{F}^{(r_1, r_2)}(\mathbf{u}, \mathbf{n}_0, L)} \right)^{v(R)} \exp \left\{ -\tau(r_1, \mathbf{R}) \left[\bar{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - \underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) \right] \right\} \right)$$

???

$$A_{\text{coarse}}(\mathbf{u}, \mathbf{n}_0, L) \equiv \prod_{r_1} \left(A_{\text{fine}}(r_1, \mathbf{u}, \mathbf{v}, \sigma_1, \mathbf{n}_0, L) \left(\frac{D^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L)}{D_{\hat{\kappa}}^{(r_1)}(\mathbf{n}_0, L)} \right)^{u_{r_1}} \exp \left\{ -\tau(r_1, \mathbf{R}) \left[\underline{D}^{(r_1)}(\mathbf{u}, \mathbf{n}_0, L) - D_{\hat{\kappa}}^{(r_1)}(\mathbf{n}_0, L) \right] \right\} \right)$$

1.9 Optimization for \hat{D} and $D_{\hat{\kappa}}$

We want to compute

$$\hat{D}^{(r_1)}(\mathbf{n}_0, L(u)) \equiv \max_{\{u | \sum u = L \wedge u_{r_1} \geq 1\}} D^{(r_1)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L))$$

and

$$D_{\hat{\kappa}}^{(r_1)}(\mathbf{n}_0, L(u)) \equiv \min_{\{u | \sum u = L \wedge u_{r_1} \geq 1\}} D^{(r_1)}(\underline{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)),$$

where

$$\begin{aligned} \bar{n}_{Ar_1}(\mathbf{u}, \mathbf{n}_0, L) &= n_A(0) + \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \max_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \\ \underline{n}_{Ar_1}(\mathbf{u}, \mathbf{n}_0, L) &= n_A(0) + \sum_{r_1'} (u_{r_1'} - \delta_{r_1 r_1'}) \left\{ \sum_{\alpha} C_{a_1 \alpha}^{r_1'} \min_{r_2'} \Delta m_{a_2 \alpha}^{r_2'} \right\} \end{aligned}$$

The essential observation is that each $D^{(r_1)}(\mathbf{n})$ function is both monotonic and convex in each \mathbf{n}_A argument, and convexity is preserved by composition with the linear functions $\bar{n}_{Ar_1}(\mathbf{u})$. A function $f(\mathbf{x})$ is convex if

$$\alpha \in [0, 1] \Rightarrow f(\alpha \mathbf{x} + (1 - \alpha) \mathbf{y}) \leq \alpha f(\mathbf{x}) + (1 - \alpha) f(\mathbf{y}).$$

Clearly this property is preserved by linear combination of functions with nonnegative weights. Since each $D^{(r_1)}(\mathbf{n})$ is a linear combination of functions $F^{(r_1 r_2)}(\mathbf{n})$ with nonnegative weights, and each $F(\mathbf{n})$ is convex and monotonic in each n_A :

XXX look up previous stoichiometry notation for this XXX

$$\begin{aligned} F^{(R)}(n) &= \prod_A (n_A!) / ((n_A - k_A^{(R)})!) \\ &= \prod_A \prod_{i=1}^{k_A} ((n_A - k_A^{(R)}) + i) = \prod_A \left(\sum_{j=0}^{k_A-1} c_j^{(R)} (n_A - k_A^{(R)})^j \right) \\ &= \prod_A \prod_{i=1}^{k_A} ((n_A - k_A^{\max}) + k_A^{\max} - k_A^{(R)} + i) = \prod_A \left(\sum_{j=0}^{k_A-1} c_j^{(R)'} (n_A - k_A^{\max})^j \right) \end{aligned}$$

(which has only positive coefficients c_j or c_j'), we know that $D^{(r_1)}(\mathbf{n})$ is convex and monotonic in each scalar variable n_A separately. However, the product in F means that it is *not* generally convex in all of its inputs jointly.

$$\bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) = n_A(0) - \Delta m_{a_1}^{r_1} + \sum_{r_1'} u_{r_1'} \Delta m_{a_1}^{r_1'} +$$

$$\Delta m_{a_1}^{r_1'} + \equiv \max_{r_2'} \Delta m_{a_1}^{r_1' r_2'}$$

Set

Then

$$\bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L) - k_A^{(R)} = \left(n_A(0) - \Delta m_{a_1}^{r_1} + - k_A^{(R)} \right) + \sum_{r_1'} u_{r_1'} \Delta m_{a_1}^{r_1'} +$$

$$F^{(R)}(\bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L)) = \prod_A \left(\sum_{j=0}^{k_A-1} c_j^{(R)} \left(n_A(0) - \Delta m_{a_1}^{r_1} + - k_A^{(R)} + \sum_{r_1'} u_{r_1'} \Delta m_{a_1}^{r_1'} + \right)^j \right)$$

$$D^{(r_1)}(\bar{n}_{* r_1}(\mathbf{u}, \mathbf{n}_0, L)) =$$

$$\sum_{r_2} \rho_R F^{(R)}(\bar{n}_{A r_1}(\mathbf{u}, \mathbf{n}_0, L)) = \sum_{r_2} \rho_R \prod_A \left(\sum_{j=0}^{k_A-1} c_j^{(R)} \left(n_A(0) - \Delta m_{a_1}^{r_1} + - k_A^{(R)} + \sum_{r_1'} u_{r_1'} \Delta m_{a_1}^{r_1'} + \right)^j \right)$$

The optimization problem is to maximize this with respect to \mathbf{u} , satisfying the linear constraints on \mathbf{u} :

$$\sum_{u_{r_1'}} u_{r_1'} = L \wedge u_{r_1} \geq 1.$$

If $n_A(0) - \Delta m_{a_1}^{r_1} + - k_A^{(R)} \geq 0$ for all A ,

$$\begin{aligned} D^{(r_1)}(\bar{n}_{* r_1}(\mathbf{u}, \mathbf{n}_0, L)) &= \\ &= \sum_{r_2} \rho_R \prod_A \left(\sum_{j=0}^{k_A-1} d_j^{(R)} \left(\sum_{r_1'} u_{r_1'} \Delta m_{a_1}^{r_1'} + \right)^j \right) \end{aligned}$$

where the d 's are still nonnegative.

Large $n_A(0)$ and/or \mathbf{u} 's:

$$F^{(R)}(\mathbf{n}) \simeq \prod_A (n_A)^{k_A^{(R)}}$$

$$D^{(r_1)}(\bar{n}_{* r_1}(\mathbf{u}, \mathbf{n}_0, L)) \simeq \sum_{r_2} \rho_R \prod_A \left(n_A(0) + \sum_{r_1'} u_{r_1'} \Delta m_{a_1}^{r_1'} + \right)^{k_A^{(R)}} + \lambda \left(\sum_{u_{r_1'}} u_{r_1'} - L \right)$$

Interior maxima, for all r_1'' :

$$-\lambda \simeq \sum_{r_2} \rho_R \sum_A k_A^{(R)} \Delta m_A^{r_1''} + \left(n_A(0) + \sum_{r_1'} u_{r_1'} \Delta m_A^{r_1'} + \right)^{k_A^{(R)}-1} \prod_{A' \neq A} \left(n_{A'}(0) + \sum_{r_1'} u_{r_1'} \Delta m_{A'}^{r_1'} + \right)^{k_{A'}^{(R)}} .$$

Find maximum numerically and track it as simulation changes $n_A(0)$ from one mega-step to another. Eg. greedy method: repeatedly increment $\sum_{r_1'} u_{r_1'}$ by one, adding to the r_1'' with the highest slope as given by the right hand side of the (approximate) derivative above. Even better, simpler, and more exact ...

1.9.1 Greedily maximize $D^{(r_1)}(\bar{n}(u))$

Even better greedy method uses *discrete derivatives*:

$$\begin{aligned} D^{(r_1)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) &= \sum_{r_2} \rho_R F^{(R)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) \\ &= \sum_{r_2} \rho_R \prod_A (\bar{n}_{Ar_1}(\mathbf{u}, \mathbf{n}_0, L))_{k_A^{(R)}} \\ &= \sum_{r_2} \rho_R \prod_A \left(n_A(0) - \Delta m_A^{r_1} + \sum_{r_1'} u_{r_1'} \Delta m_A^{r_1'} + \right)_{k_A^{(R)}} \end{aligned}$$

Take forward differences:

$$\begin{aligned} \frac{\Delta}{\Delta u_{r_1''}} \left[D^{(r_1)}(\bar{n}_{*r_1}(\mathbf{u}, \mathbf{n}_0, L)) + \lambda \left(\sum_{u_{r_1'}} u_{r_1'} - L \right) \right] \\ = \lambda + \frac{\Delta D^{(r_1)}}{\Delta u_{r_1''}} \end{aligned}$$

where

$$\begin{aligned} \frac{\Delta D^{(r_1)}}{\Delta u_{r_1''}} &= \sum_{r_2} \rho_R \sum_A k_A^{(R)} \Delta m_A^{r_1''} + \left(n_A(0) - \Delta m_A^{r_1} + \sum_{r_1'} u_{r_1'} \Delta m_A^{r_1'} + \right)_{k_A^{(R)}-1} \\ &\quad \prod_{A' \neq A} \left(n_{A'}(0) - \Delta m_{A'}^{r_1} + \sum_{r_1'} u_{r_1'} \Delta m_{A'}^{r_1'} + \right)_{k_{A'}^{(R)}} \end{aligned}$$

The greedy procedure is: first evaluate $\frac{\Delta D^{(r_1)}}{\Delta u_{r_1''}}(u=0)$, then set $u_{r_1} = 1$, then repeatedly (a) update $\frac{\Delta D^{(r_1)}}{\Delta u_{r_1''}}$ and (b) increment the $u_{r_1''}$ with the largest discrete derivative, until $\sum_{u_{r_1'}} u_{r_1'} = L$. Cheaper variant: instead of incrementing the winning $u_{r_1''}$ by one, increment it by \sqrt{L} so that only \sqrt{L} step of the algorithm need to be taken. This may balance costs with the other parts of the algorithm. Even more approximate and affordable: increment winning u by L/c , for c steps eg $c = 10$.

In this way, find maximum numerically and track it as simulation changes $n_A(0)$ from one mega-step to another.

1.9.2 Minimize $D^{(r_1)}(\underline{n}(u))$

Minimum of $D^{(r_1)}(\underline{n}_{*r_1}(u, n_0, L))$:

$$\Delta m_{a_1 a_2}^{r_1' -} \equiv \min_{r_2'} \Delta m_{a_1 a_2}^{r_1' r_2'}$$

$$D^{(r_1)}(\underline{n}_{*r_1}(u, n_0, L)) =$$

$$\sum_{r_2} \rho_R F^{(R)}(\underline{n}_{Ar_1}(u, n_0, L)) = \sum_{r_2} \rho_R \prod_A \left(\sum_{j=0}^{k_A-1} c_j^{(R)} \left(n_A(0) - \Delta m_A^{r_1 -} - k_A^{(R)} + \sum_{r_1'} u_{r_1'} \Delta m_A^{r_1' -} \right)^j \right)$$

Look for minima at the boundaries, i.e. the extremes of $\underline{n}_{Ar_1}(u, n_0, L)$.

Or (probably better), use greedy discrete optimization as above, using these discrete derivatives:

$$\frac{\Delta D^{(r_1)}}{\Delta u_{r_1''}} = \sum_{r_2} \rho_R \sum_A k_A^{(R)} \Delta m_A^{r_1''} - \left(n_A(0) - \Delta m_A^{r_1 -} + \sum_{r_1'} u_{r_1'} \Delta m_A^{r_1' -} \right)_{k_A^{(R)}-1}$$

$$\prod_{A' \neq A} \left(n_A(0) - \Delta m_A^{r_1 -} + \sum_{r_1'} u_{r_1'} \Delta m_A^{r_1' -} \right)_{k_A^{(R)}}$$

2 Old Junk

3 Same derivation as 1.1 but with time component (DO--8/9/09)

4 Algorithm

HiERLeap6_V1.nb

A Appendix Head...

Appendix text begins here...